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To: Examiner Kagnew Gebreyesus **From:** Gary Baker

USPTO, Group 1656

Fax: 571 273-2937; 571-273-8300 **Date:** April 2, 2009

Phone: **Pages:** 3 including cover

Re: USSN 10/575,991 **our file:** 54-000711US

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Dear Examiner Gebreyesus,

Attached is a proposed amendment to claim 31 in the above-cited case. Also included is a brief rationale supporting enablement of the claim. Let me know when you would like to discuss the proper scope of claims in this case.

Best regards,

Gary

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April 2, 2009
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Scripps Research Institute/Novartis
Site-Specific Incorporation of Redox Active Amino Acids into Proteins.

Dear Examiner Gebreyesus,

In our recent discussion, I agreed to prepare amendments to independent claim 31 as a starting point for a discussion directed to identify a reasonable claim scope in the above identified case.

The independent claim 31 has been directed to the aspect of a protein product comprising two or more redox active unnatural amino acids. Applicants have screened a library of RSs mutated at identified amino acids at positions that interact with amino acid side chains in the binding pocket. Structures have been identified that selectively bind a meta-substituted analog of phenylalanine. Selection in the embodiment focused on amino acids at positions (32, 67, 70, 155, 158 and 167) interacting at the meta position of the unnatural amino acid. Several journal articles have shown that an RS mutated to selectively charge with an unnatural amino acid having a certain side chain structure will also charge with another unnatural amino acid of similar structure. See, e.g., Deiters, JACS 125: 11782-3, (2003); and Xu, JACS 126: 15654-5, (2004). Therefore, it is reasonable to expect the identified structures to function with the listed meta-substituted unnatural amino acids.

Of course, because the general alpha helix, beta sheet, turns structure of the MjTyrRS (from which the present RS is derived) is known, one of skill can readily provide a high percentage of active redox charging variants by conservative substitution, e.g., with amino acids known to retain the known structures. For example, methionine, alanine, leucine, uncharged glutamate, and lysine ("MALEK") have long been known retain alpha helix structures. Regarding beta sheet structures found in active proteins, large aromatic residues (Tyr, Phe and Trp) and β-branched amino acids (Thr, Val, Ile) are favored to be found in β strands in the middle of β sheets. Most such intelligent substitutions, even multiple substitutions, would retain some or all activity. It would not be undue experimentation in the art to discard the few failures, or even a worst case majority of failures to identify additional functioning RSs based on the given functional RS retaining the key given structures. Therefore, it should be more than reasonable to deem a 95% identity to be enabled, including retention of key identified residues.

In the previous Response of December 16, 2008, I had presented a variety of new dependent claims offering the Office the opportunity of pointing out what it deems enabled matter. From our conversation of April 1, I felt you may find a claim providing a combination of described elements from those dependent claims to be enabled. Below, I present a proposed claim for discussion including a combination of aspects from new claims 49 and 50:

31. (Proposed) A composition comprising a protein, wherein the protein comprises two or more redox active amino acids selected from the group consisting of: a 3,4-dihydroxy-L-phenyalanine (DHP), a 3,4,5-trihydroxy-L-phenylalanine, a 3-nitro-tyrosine, and a 4-nitro-phenylalanine~~, and a 3-thiol-tyrosine~~;

the composition further comprising:

i) at least one orthogonal tRNA (O-tRNA)~~, wherein the O-tRNA comprises or is encoded by a polynucleotide sequence as set forth in SEQ ID NO: 2;~~

ii) at least one orthogonal aminoacyl-tRNA synthetase (O-RS) comprising a Leu amino acid in a position of the O-RS corresponding to Tyr32 of SEQ ID NO: 4, a Ser amino acid residue in a position of the O-RS corresponding to Ala67 of SEQ ID NO: 4, an Asn amino acid residue in a position of the O-RS corresponding to His70 of SEQ ID NO: 4, and a Gln residue in a position of the O-RS corresponding to Ala167 of SEQ ID NO: 4, and SEQ ID NO: 4 is the wild type sequence; wherein the O-RS comprises at least 95% identity to the RS of SEQ ID NO: 1 ~~or derived from an RS selected from the group consisting of: an *Archaeoglobus fulgidus* synthetase, a *Methanosarcina mazei* synthetase, a *Methanobacterium thermoautotrophicum* synthetase, and a *Pyrococcus horikoshii* synthetase,~~ wherein the O-RS preferentially aminoacylates the O-tRNA with one or more of the redox active amino acids; and

iii) a nucleic acid that encodes the protein, wherein the nucleic acid comprises at least two selector codons that are recognized by the O-tRNA.

Please let me know what you think of the claims. Would this combination of claim elements be deemed allowable? If not, how might it be adjusted?

Best regards,

Gary Baker
41,595